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Note: This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 02/08/2008). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

47114034 Meyer, B.; Ripperger, R. (2006) The Metabolism of [Phenyl-UL-^{14}C]-Isoxaflutole in Corn with Post-Emergence Application. Project Number: MEUBY003, M/268739/01/1. Unpublished study prepared by Bayer Corp. 59 p.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a study investigating the metabolism of [phenyl-UL-^{14}C]isoxaflutole in corn when applied with the safener AE 001789 (cyprosulfamide). The radiolabeled test substance was mixed with suspension-concentrate (SC) formulation blank and the safener cyprosulfamide, diluted with tap water, and applied as a single foliar broadcast application to corn plants grown in buckets indoors. After treatment, the buckets were moved to a covered outdoor patio area. The application was made at 0.19 lb ai/A (211 g ai/ha) at the V2 growth stage. Samples of corn forage and sweet corn kernel plus cob with husk removed (K+CWHR) were harvested at 75 days after application (milk stage), and samples of mature corn grain and stover were harvested at maturity, 106 days after application.

Total radioactive residues (TRR) in corn matrices treated with radiolabeled isoxaflutole, determined by combustion/liquid-scintillation counting (LSC), were 0.081 ppm in corn forage, 0.010 ppm in corn K+CWHR, 0.015 ppm in mature corn grain, and 0.120 ppm in corn stover. Extraction with water and acetonitrile (ACN) released the majority of the radioactivity from samples of all corn matrices: 92.9% TRR from corn forage, 96.3% TRR from corn K+CWHR, 77.3% TRR from mature corn grain, and 87.9% TRR from corn stover. Additional residues were released from stover samples using accelerated solvent extraction (ASE) with 0.5 M H_2SO_4:ACN (1:1, v:v) and 0.5 M NH_4OH:ACN (1:1, v:v), 4.3% TRR and 1.5% TRR, respectively. Remaining nonextractable residues accounted for 7.1% TRR (0.006 ppm) in corn forage, 3.7% TRR (<0.001 ppm) in corn K+CWHR, 22.7% TRR (0.004 ppm) in mature corn grain, and 6.3% TRR (0.008 ppm) in corn stover. Because the petitioner normalized radioactivity levels, accountabilities were 100% in all matrices; recoveries prior to normalization were 86-115%. The extraction procedures adequately extracted the majority of residues from corn matrices. Residues were identified by high-performance liquid chromatography (HPLC), and the identity of the major metabolite was confirmed in stover extract by liquid chromatography/mass

spectroscopy/mass spectroscopy (LC/MS/MS). Because all experimental work was completed within 6 months of sample collection, supporting storage stability data are not required.

Approximately 67-73% of the TRR were identified in corn matrices. Isoxaflutole was not identified in any matrix. The major residue identified was RPA 203328 (isoxaflutole acid), accounting for 67.2% TRR (0.056 ppm) in corn forage, 60.9% TRR (0.005 ppm) in corn K+CWHR, 63.0% TRR (0.010 ppm) in corn grain, and 63.3% TRR (0.076 ppm) in corn stover. A portion of the RPA 203328 identified in corn forage and stover was found after base hydrolysis of aqueous soluble residues (15.4% TRR in forage and 4.1% TRR in stover). The only other identified metabolite was RPA 202248 (isoxaflutole diketonitrile), which accounted for 6.5% TRR (<0.001 ppm) in corn K+CWHR, 9.8% TRR (0.001 ppm) in mature corn grain, and 4.3% TRR (0.005 ppm) in corn stover; RPA 202248 was not identified in corn forage. The remainder of the radioactivity consisted of unknowns, totaling ≤12% TRR (≤0.014 ppm), and aqueous soluble fractions, totaling ≤26% TRR (≤0.016 ppm).

Based on the submitted corn metabolism study, the petitioner proposed that metabolism of isoxaflutole in corn proceeds via cleavage of the isoxazole ring resulting in RPA 202248, which is isomeric with the parent. RPA 203328 results from cleavage of the carbonyl bridge and loss of the complete isoxazole moiety. The same metabolites were observed in an earlier corn study in which isoxaflutole was applied using both preplant incorporated and preemergence methods, without the addition of the safener cyprosulfamide (DP#s 214199 and 214212, 12/7/95, P. Errico). In that study, RPA 203328 was the major metabolite in all matrices (field corn forage, fodder, and grain), at 64-91% TRR. RPA 202248 was found in all matrices at <1% TRR, with the exception of grain from the preplant incorporated trial where RPA 202248 was found at 7.5% TRR. Isoxaflutole was not found in any matrix.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the plant metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, DP# 340598.

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance, and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Isoxaflutole is an isoxazole herbicide (Group 27) registered for control of broadleaf and grass weeds in corn. Bayer CropScience has developed a new herbicide safener (AE 0001789; cyprosulfamide) for use on corn in conjunction with isoxaflutole. The chemical structure and nomenclature of isoxaflutole and its metabolites RPA202248 and RPA 203328 are presented in

Table A.1. The physicochemical properties of the technical grade of isoxaflutole are presented in Table A.2.

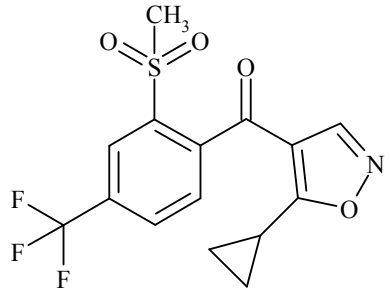
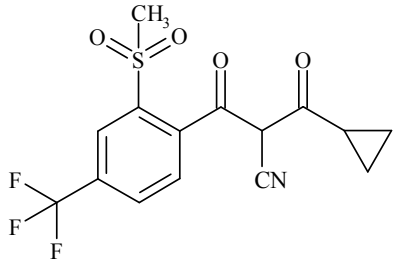
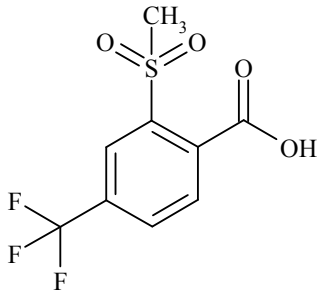
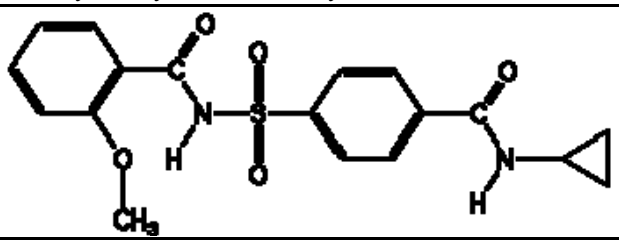
TABLE A.1. Test Compound Nomenclature.	
Compound	
Common name	Isoxaflutole
Company experimental name	RPA 201772; AE B197278
IUPAC name	5-cyclopropyl-4-(2-mesyl-4-trifluoromethylbenzoyl)isoxazole
CAS name	(5-cyclopropyl-4-isoxazolyl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone
CAS registry number	141112-29-0
End-use product (EP)	SC 480 Herbicide (EPA File Symbol No. 264-RNAT; 2.0 lb/gal FlC formulation) SC 465 Herbicide (EPA File Symbol No. 264-RNAA; 1.88 lb/gal FlC formulation)
Compound	
Common name	Isoxaflutole diketonitrile; RPA 202248
Chemical name	1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione
Compound	
Common name	Isoxaflutole acid; RPA 203328
Chemical name	2-methylsulfonyl-4-trifluoromethyl benzoic acid
Compound	

TABLE A.1. Test Compound Nomenclature.	
Common name	Cyprosulfamide; AE 0001789
Chemical name	*N*-[[4-[(cyclopropylamino)carbonyl]phenyl]sulfonyl]-2-methoxybenzamide

TABLE A.2. Physicochemical Properties of Isoxaflutole.		
Parameter	Value	Reference
Melting range	135-136 °C	DP#s 214199 & 214212, 12/7/95, P. Errico
pH	4.6 at 25 ºC (1% w:v aqueous suspension containing 2% acetonitrile, v:v)	
Density	1.416 at 20 ºC	
Water solubility	6.2 mg/L at 20 °C (pH 5.5)	
Solvent solubility	Solvent / g/L at room temperature Methylene chloride 346 Acetone 293 Acetonitrile 233 Ethyl acetate 142 Toluene 31.2 Methanol 13.8 Octanol 0.76 Hexane 0.1	
Vapor pressure	1.0×10^{-6} Pa at 20 °C	
Dissociation constant, pK_a	Not determined	
Octanol/water partition coefficient	219 (log P = 2.34) at 20 ºC	
UV/visible absorption spectrum	$\lambda_1 = 204$ $\lambda_2 = 269$	MRID 47114035

B. EXPERIMENTAL DESIGN

B.1. Test Site and Crop Information

The field test site was located at Bayer Research Park (Stilwell, KS). A summary of the test site information is provided in Table B.1.1, and a summary of the crop information is provided in Table B.1.2. Corn plants were grown in buckets (28.6 cm diameter x 36.8 cm deep) in a sandy loam soil fertilized with Osmocote® 14-14-14. After emergence, the plants were thinned to one plant per bucket. The plants were maintained in a greenhouse until after treatment, at which time they were placed in a containment trough on a covered outdoor patio area. The plants were maintained following normal agricultural practices, and maintenance pesticides and irrigation were applied as needed. Daily temperature maxima and minima for the outdoor portion of the study were provided.

Samples of corn forage and sweet corn K+CWHR were harvested 75 days after application (milk stage) by cutting the plants at the base and separating the ears from the rest of the plant; the husks and silks were removed from the ears and added to the forage samples. Samples of corn grain and stover were harvested at 106 days after application (maturity) by cutting the plants at the base and separating the ears from the rest of the plant; the husks and silks were removed from the ears and added to the stover samples, and then the grain was removed from the cobs. Forage

and stover were grouped into three samples; for K+CWHR and grain, ears of all plants were combined into one sample.

TABLE B.1.1. Test Site Information.

Type	Method	Soil characteristics[1]			
		Type	%OM	pH	CEC
Foliar Treatment	Hand-held, pump-action sprayer; applied as evenly as possible to each pot.	Sandy Loam	1.7	6.4	9.9 meq/100 g

[1] OM = Organic matter, CEC = Cation-exchange capacity.

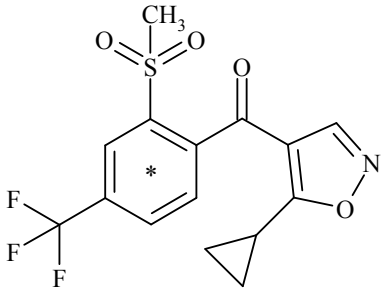
TABLE B.1.2. Crop Information.

Crop; crop group	Variety	Growth stage at application	Growth stage at harvest	Harvested Matrix
Corn; Grain, cereal, group 15, and Grain, cereal, forage, fodder, and straw, group 16	N7070 BT	V2	R3 (milk stage)	Forage
				Sweet corn K+CWHR
			R6 (mature)	Stover
				Grain

B.2. Test Materials

The radiolabeled test substance was mixed with formulation blank and cyprosulfamide and diluted with tap water for application. The characteristics of the test substance are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics.

Chemical structure	
Radiolabel position	[phenyl-UL-^{14}C]isoxaflutole
Lot No.	2004BRP048-172
Purity	100% (radio-HPLC)
Specific activity	18.35 mCi/mmol (51.1 µCi/mg, 1.89 MBq/mg)

B.3. Study Use Pattern

The formulated test substance was applied as a single broadcast foliar application at the V2 growth stage at a rate of 0.19 lb ai/A (211 g ai/ha). Applications were made using a hand-held pump-action sprayer. Details of the study use pattern are presented in Table B.3.1.

TABLE B.3.1. Use Pattern Information.	
Chemical name	[phenyl-UL-^{14}C]isoxaflutole
Application method	The test substance was mixed with suspension concentrate formulation blank and the safener cyprosulfamide, diluted with tap water, and applied as a single foliar broadcast application using a hand-held pump-action sprayer.
Application rate	0.19 lb ai/A (211 g ai/ha)
Number of applications	1
Timing of applications	Growth stage V2
PHI	Forage and K+CWHR: 75 days Grain and stover: 106 days

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

The analytical phase was conducted on-site at Bayer Research Park. All samples were homogenized in the presence of dry ice and then stored frozen (<-20 ºC) until analysis.

Forage samples were extracted (3x) with ACN and the extracts combined; the process was repeated using ACN:water (4:1, v:v) and ACN:water (1:1, v:v). Portions of each extract were combined and the ACN was removed by evaporation. The remaining aqueous extract was adjusted to pH 2 using concentrated HCl and partitioned with ethyl acetate. The ethyl acetate layer was concentrated and further partitioned between hexane and methanol:water (9:1,v:v). A portion of the methanol/water phase was concentrated and further fractionated using a C18 solid-phase extraction (SPE) cartridge, eluting with increasing concentrations of ACN in 0.1% trifluoroacetic acid (TFA). The ACN:0.1% TFA (1:1, v:v) fraction, containing the major portion of the radioactivity, was concentrated and analyzed by HPLC. The aqueous fraction arising from ethyl acetate partitioning was separately subjected to acid hydrolysis using 1 N HCl (at 60 ºC for 24 hours) and base hydrolysis using 1 N NaOH (at 50 ºC for 17 hours). The acid hydrolysate was partitioned with ethyl acetate, and the ethyl acetate phase was analyzed by HPLC. The base hydrolysate was partitioned with dichloromethane (DCM) at both basic and acidic pH. The acidic DCM extract, containing the major portion of the radioactivity, was concentrated and analyzed by HPLC.

Samples of sweet corn K+CWHR were extracted (3x) with ACN, ACN:water (4:1, v:v), and ACN:water (1:1, v:v) as for forage samples; portions of each extract were combined and subjected to the evaporation, acidification, and ethyl acetate, hexane, and methanol:water (9:1, v:v) partitioning steps outlined above. After concentration of the ethyl acetate extract, appreciable solid material was left undissolved; a series of solvents (methanol, acetone, n-butanol, and 0.1 N NaOH) were used to solubilize the residue for radioassay. As for forage, a portion of the methanol/water extract was concentrated and further fractionated using a C18 SPE cartridge, eluting with increasing concentrations of ACN in 0.1% TFA. Fractions were pooled and concentrated for HPLC analysis.

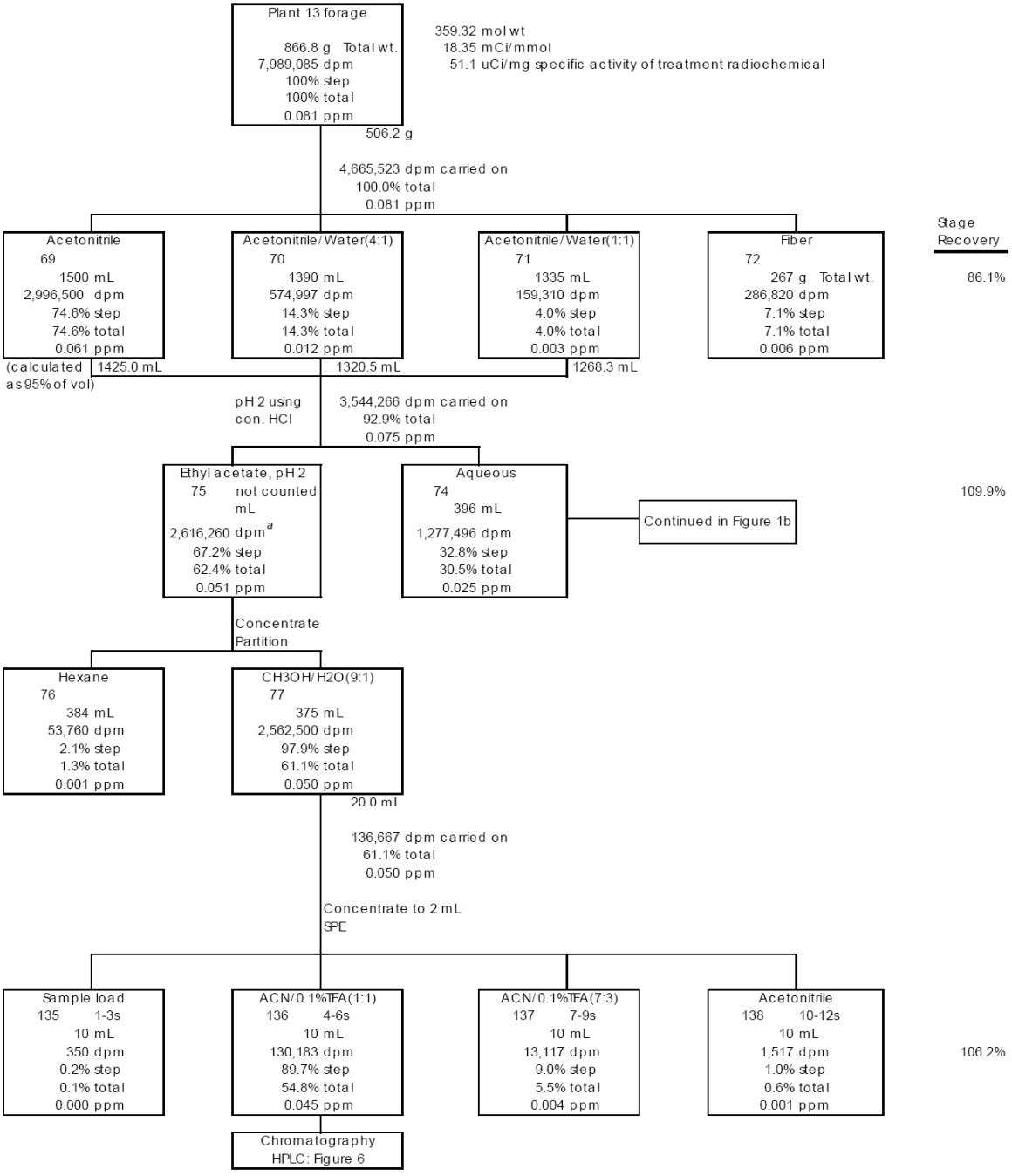
Grain samples were extracted with ACN and ACN/water in the same manner as forage and K+CWHR samples. The combined extracts were cleaned up on a C18 SPE cartridge and then concentrated to remove the ACN. The remaining aqueous solution was subjected to the acidification and ethyl acetate, hexane, and methanol:water (9:1, v:v) partitioning steps outlined above. The methanol/water extract was concentrated for HPLC analysis.

Stover samples were extracted with ACN and ACN/water in the manner outlined above and the combined extract cleaned up on a C18 SPE cartridge. The extract was concentrated to remove acetonitrile and the remaining aqueous solution subjected to the acidification and partitioning steps as for the other matrices. The methanol/water extract was concentrated for HPLC analysis. The aqueous fraction arising from ethyl acetate partitioning was subjected to 1 N NaOH base hydrolysis (at 50 ºC for 17 hours) and the resulting hydrolysate was partitioned with DCM at both basic and acidic pH. The acidic DCM extract, containing the majority of the radioactivity, was concentrated for HPLC analysis.

The nonextractable residues of stover remaining after ACN/water extraction were subjected to ASE with 0.5 M H_2SO_4:ACN (1:1, v:v) at 75 ºC. The solids were then subjected to ASE extraction with 0.5 M NH_4OH: ACN (1:1, v:v) at 75 ºC.

Flow charts of the extraction procedures for forage, sweet corn K+CWHR, grain, and stover are presented below. The flow charts were copied without alteration from MRID 47114034.

Figure B.4.1.1. Extraction Flowchart for Forage, Primary Extraction.



[a] Fraction 75 was not sampled for LSC. Dpm shown is sum of Fration 76 & 77.

Figure B.4.1.2. Extraction Flowchart for Forage, Base Hydrolysis of Aqueous Soluble Fraction.

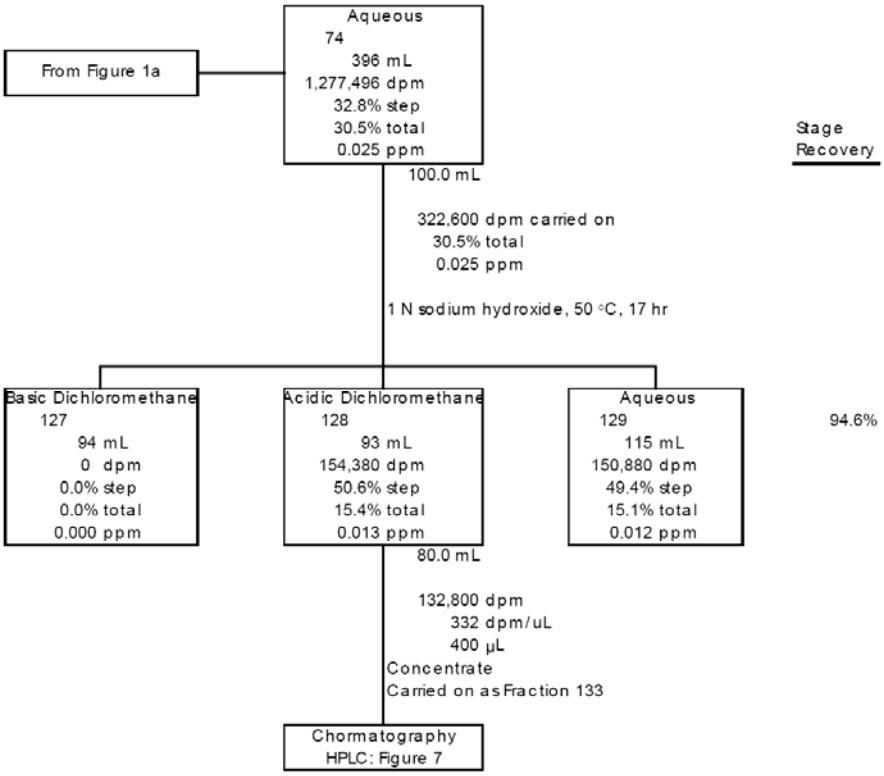


Figure B.4.1.3. Extraction Flowchart for Sweet Corn K+CWHR.

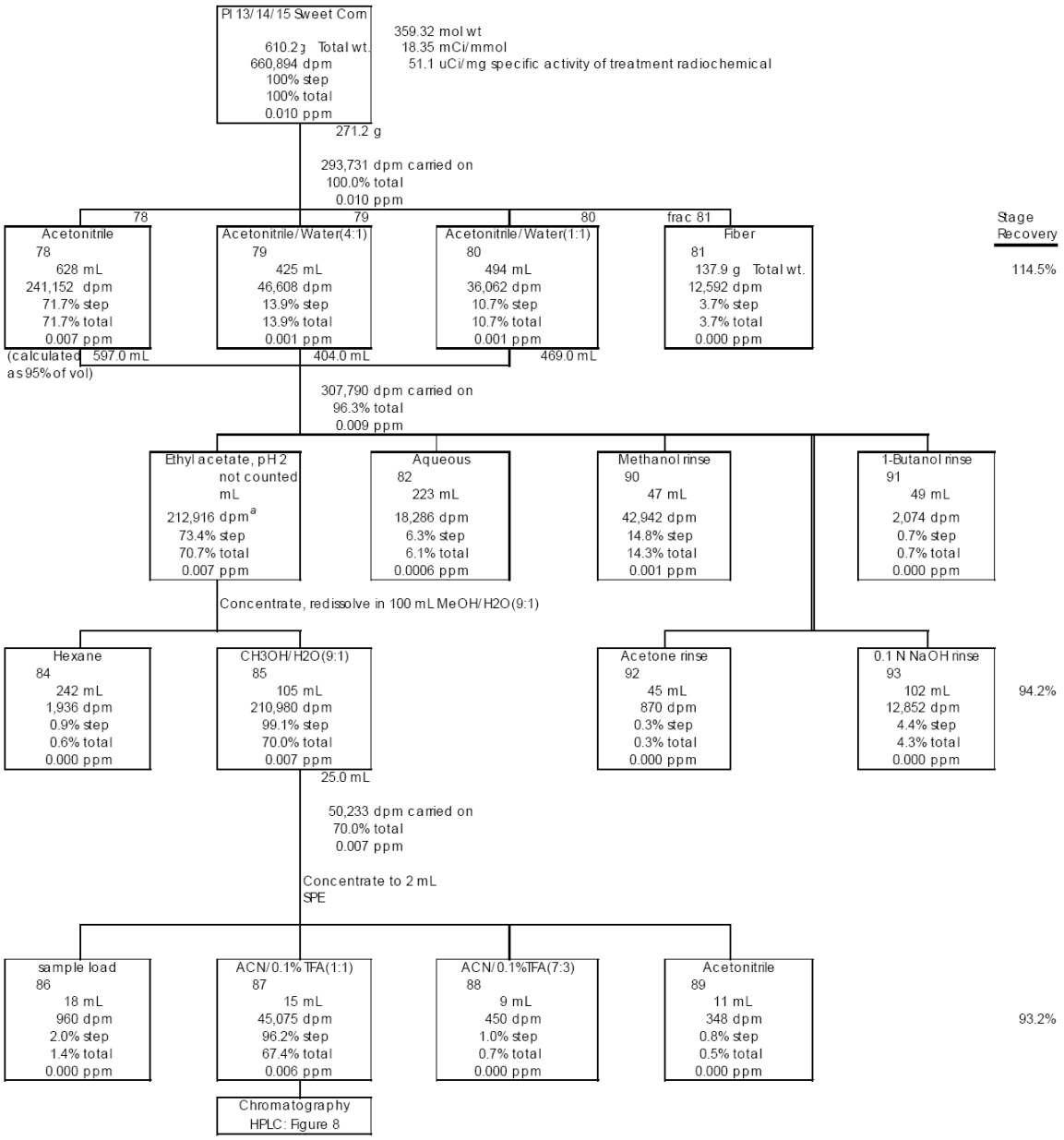


Figure B.4.1.4. Extraction Flowchart for Grain.

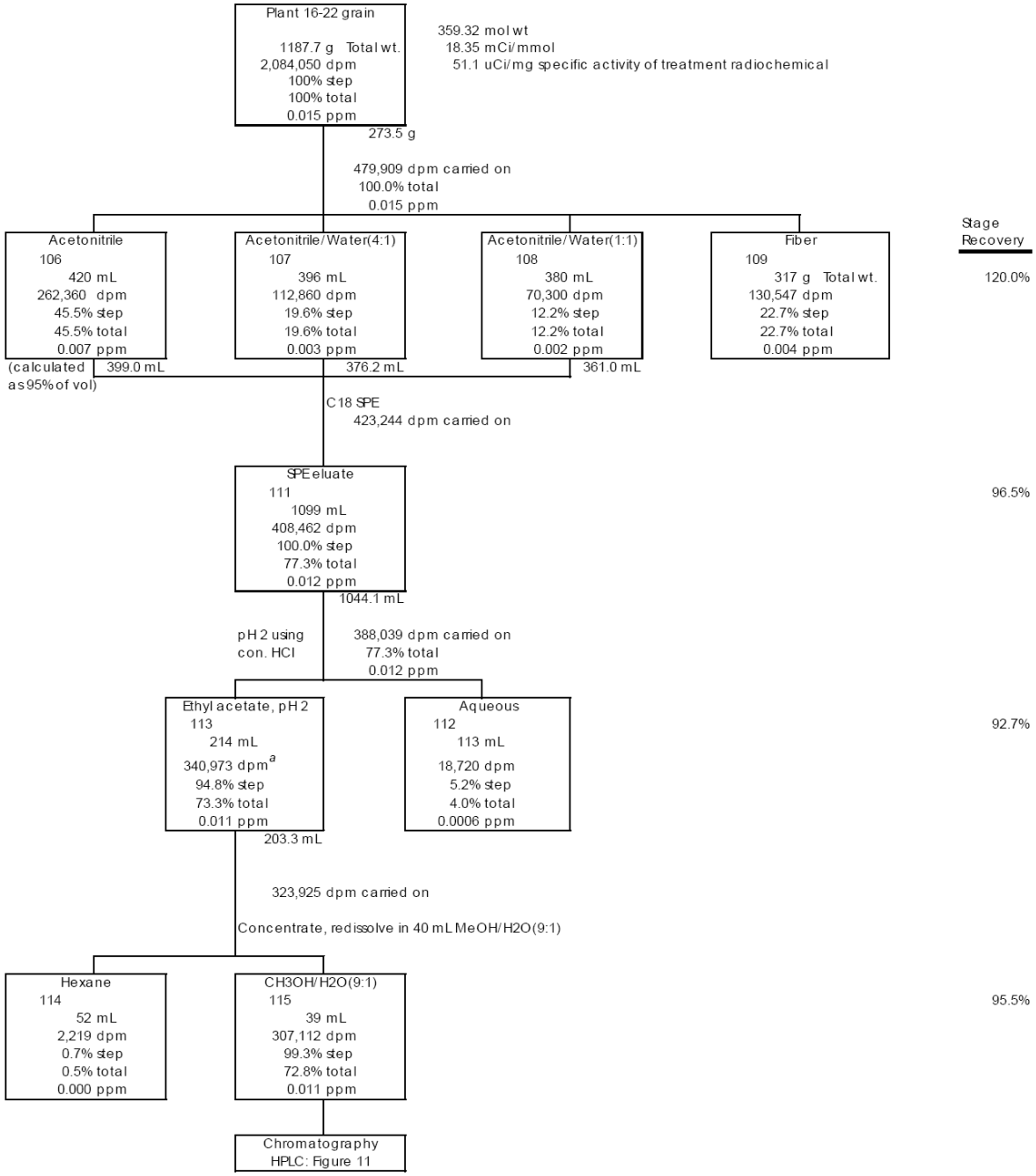


Figure B.4.1.5. Extraction Flowchart for Stover, Primary Extraction.

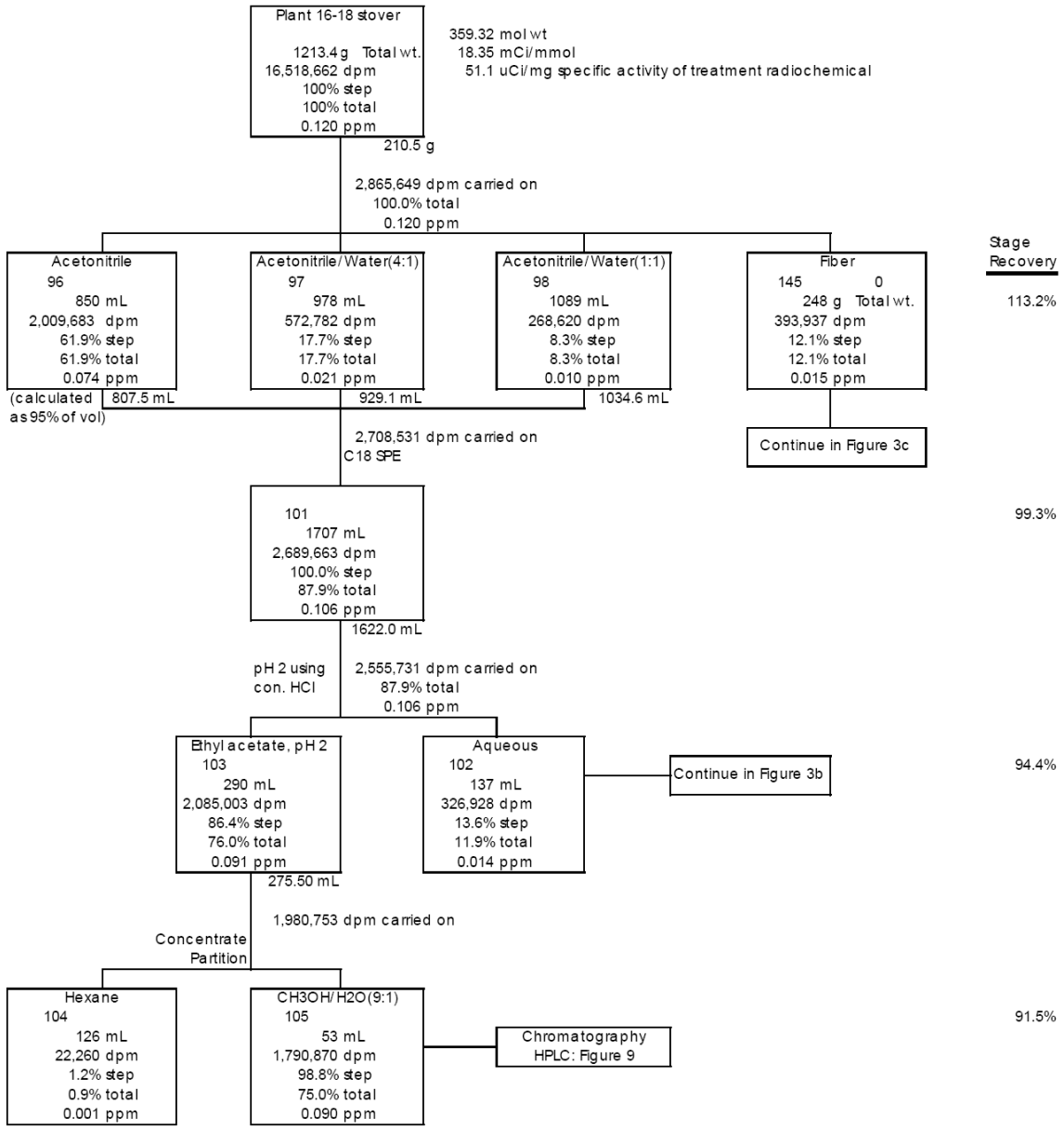


Figure B.4.1.6. Extraction Flowchart for Stover, Base Hydrolysis of Aqueous Soluble Fraction.

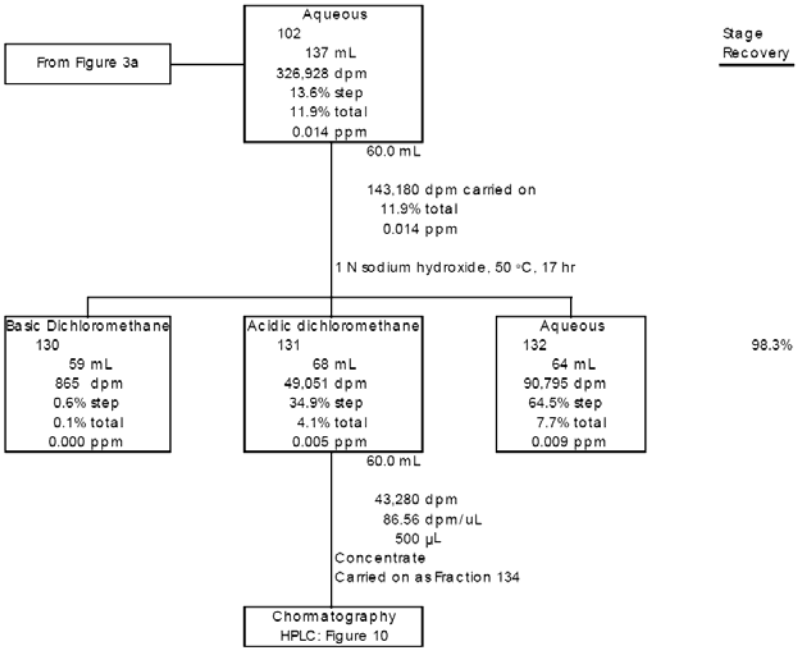
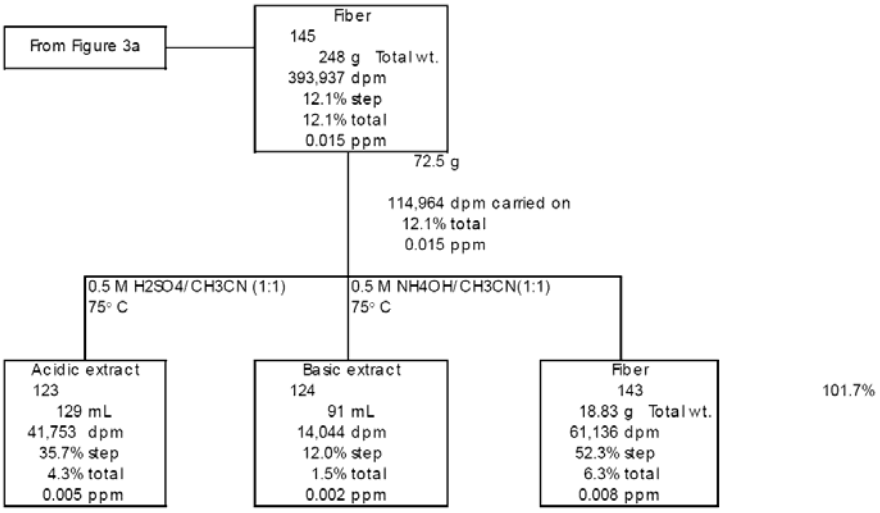


Figure B.4.1.7. Extraction Flowchart for Stover, ASE Extraction.



B.4.2. Analytical Methodology

TRR were determined in solid samples and nonextractable residues by combustion/LSC. For forage and stover, TRR were determined in each of the three samples collected; however, only one sample was carried through to identification and characterization. TRR in extracts were determined by LSC. For LSC measurements, any determination greater than the corresponding

background radioactivity was considered to be detectable. The LOQ was defined as the sensitivity at twice background, and calculated to be 0.005 ppm for solid samples.

Sample extracts and hydrolysates were analyzed by HPLC on a system equipped with a variable wavelength ultraviolet (UV) detector and a radioactivity detector. The petitioner reported that when fraction collection was required, collections were performed by hand. Analyses were conducted using a C18 column and a gradient mobile phase of 0.1% aqueous TFA and ACN. Metabolites were identified by comparison of retention times with those of reference standards; the reference standards used in the study are listed in Appendix I.

LC/MS/MS analysis of standards and isolated RPA 203328 was performed using a C18 column, a gradient mobile phase of 0.1% formic acid and methanol, and MS detection with electrospray interface in the negative-ion mode.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for corn matrices are presented in Table C.1. The petitioner provided the dates of sampling, combustion, extraction, and HPLC analysis of main extract for all matrices. The main extracts of each matrix were analyzed within 33 days of collection, and all experimental work was completed within 6 months of sample collection. Supporting storage stability data are not required for the submitted study.

TRR in corn matrices, determined by combustion/LSC, are reported in Table C.2.1. Following a single broadcast foliar application of [phenyl-UL-^{14}C]isoxaflutole at 0.19 lb ai/A, TRR were 0.081 ppm in corn forage, 0.010 ppm in corn K+CWHR, 0.015 ppm in corn grain, and 0.120 ppm in corn stover. These values are the TRR values for those samples upon which analyses were conducted. TRR were determined on two additional samples each for corn forage and corn stover; mean TRR values for forage and stover were 0.134 ppm and 0.100 ppm, respectively.

The distribution of radioactivity in corn matrices is presented in Table C.2.2. Extraction with ACN and water released the majority of the radioactivity from all samples of corn forage, K+CWHR, grain, and stover: 92.9% TRR from corn forage, 96.3% TRR from corn K+CWHR, 77.3% TRR from mature corn grain, and 87.9% TRR from corn stover. Acidification of the extracts followed by ethyl acetate partitioning yielded the bulk of the radioactivity in the ethyl acetate phase: 62.4% TRR for corn forage, 70.7% TRR for corn K+CWHR, 73.3% TRR for corn grain, and 76.0% TRR for corn stover.

Additional residues were released from stover samples by ASE extraction with 0.5 M H_2SO_4:ACN (1:1, v:v) and with 0.5 M NH_4OH:ACN (1:1, v:v), , 4.3% TRR and 1.5% TRR, respectively. Remaining nonextractable residues accounted for 7.1% TRR (0.006 ppm) in corn forage, 3.7% TRR (<0.001 ppm) in corn K+CWHR, 22.7% TRR (0.004 ppm) in mature corn grain, and 6.3% TRR (0.008 ppm) in corn stover. Because the petitioner normalized radioactivity levels, accountabilities were 100% in all matrices. Recoveries prior to normalization were 86-115%.

The characterization and identification of residues in corn matrices are summarized in Table C.2.3. Residues were identified by HPLC. Approximately 67-73% of the TRR were identified in corn matrices. Isoxaflutole was not identified in any matrix. The major residue identified was RPA 203328, accounting for 67.2% TRR (0.056 ppm) in corn forage, 60.9% TRR (0.005 ppm) in corn K+CWHR, 63.0% TRR (0.010 ppm) in corn grain, and 63.3% TRR (0.076 ppm) in corn stover. A portion of the RPA 203328 identified in corn forage and stover was found after base hydrolysis of aqueous soluble residues (15.4% TRR in forage and 4.1% TRR in stover). The only other identified metabolite was RPA 202248, which accounted for 6.5% TRR (<0.001 ppm) in corn K+CWHR, 9.8% TRR (0.001 ppm) in mature corn grain, and 4.3% TRR (0.005 ppm) in corn stover; RPA 202248 was not identified in corn forage. The remainder of the radioactivity consisted of unknowns, totaling ≤12% TRR (≤0.014 ppm), and aqueous soluble fractions, totaling ≤26% TRR (≤0.016 ppm).

To confirm the identification of RPA 203328, the petitioner isolated this metabolite from corn stover and conducted LC/MS/MS analyses. The MS spectrum matched that of a reference standard of RPA 203328.

For corn forage, the aqueous fractions following ethyl acetate partitioning were analyzed directly by HPLC prior to separate acid and base hydrolysis. HPLC analysis of the aqueous fraction revealed two major peaks which did not match any reference standards (quantitative data not reported). An aliquot of the aqueous fraction was then subjected to acid hydrolysis, and the hydrolysate partitioned with ethyl acetate; HPLC analysis of the ethyl acetate phase yielded multiple peaks (quantitative data not reported). The results of base hydrolysis of the aqueous fraction are reported in Table C.2.1.

C.1. Storage Stability

The petitioner provided the dates of sampling and HPLC analysis for all matrices. Samples were combusted within 17 days of collection, and were extracted within 11 days of collection. HPLC analysis of extracts was conducted within 22 days of extraction for all matrices. The petitioner only provided analysis dates for the main extracts of each matrix; no other analysis dates were provided. However, based on sample collection dates and the reported date of experimental termination, all experimental work was completed within 6 months of sample collection. Therefore, supporting storage stability data are not required for the submitted study.

TABLE C.1. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Forage	<-20	17 days (0.6 months)	None submitted; not required.
Corn K+CWHR		17 days (0.6 months	
Grain		33 days (1.1 months)	
Stover		12 days (0.4 months)	

[1] Storage duration from sample collection to HPLC analysis of main extract.

C.2. Identification, Characterization, and Distribution of Residues

TABLE C.2.1. TRR in Corn Matrices.

Matrix	Application rate (lb ai/A)	PHI (days)	[phenyl-UL-^{14}C]isoxaflutole ppm
Forage	0.19	75	0.081[1], 0.156, 0.164 (average = 0.134)
Corn K+CWHR		75	0.010
Grain		106	0.015
Stover		106	0.120[1], 0.101, 0.078 (average = 0.100)

[1] Sample used for residue characterization/identification.

TABLE C.2.2. Distribution of the Parent and the Metabolites in Corn Matrices Following Application of [Phenyl-UL-^{14}C]Isoxaflutole at 0.19 lb ai/A.[1]

Metabolite Fraction	Corn Forage		Corn K+CWHR		Corn Grain		Corn Stover	
	TRR = 0.081 ppm		TRR = 0.010 ppm		TRR = 0.015 ppm		TRR = 0.120 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Acetonitrile/water	92.9	0.075	96.3	0.009	77.3	0.012	87.9	0.105
Ethyl acetate soluble	62.4	0.051	70.7	0.007	73.3	0.011	76.0	0.091
Hexane	1.3	0.001	0.6	<0.001	0.5	<0.001	0.9	0.001
Methanol:H_2O (9:1, v:v)	61.1	0.050	70.0	0.007	72.8	0.011	75.0	0.090
RPA 203328					63.0	0.010	59.2	0.071
RPA 202248					9.8	0.001	4.0	0.005
Unknowns					--	--	11.8	0.005
ACN/0.1% TFA (1:1, v:v)	54.8	0.045	67.4	0.006				
RPA 203328	51.8	0.043	60.9	0.005				
RPA 202248	--	--	6.5	<0.001				
Unknowns	3.0	0.002	--	--				
ACN/0.1% TFA (7:3, v:v)	5.5	0.004	0.7	<0.001				
ACN	0.6	0.001	0.5	<0.001				
Methanol rinse			14.3	0.001				
Acetone rinse			0.3	<0.001				
0.1 N NaOH rinse			4.3	<0.001				
1-Butanol rinse			0.7	<0.001				
Aqueous soluble	30.5	0.025	6.1	<0.001	4.0	0.001	11.9	0.014
Base hydrolysate	Not reported						Not reported	
Basic DCM	0	0.0					0.1	<0.001
Acidic DCM	15.4	0.013					4.1	0.005
RPA 203328	15.4	0.013					4.1	0.005
Aqueous	15.1	0.012					7.7	0.009
Unextractable	7.1	0.006	3.7	<0.001	22.7	0.004	12.1	0.015
Acidic ASE extract							4.3	0.005
Basic ASE extract							1.5	0.002
Unextractable							6.3	0.008

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Corn Matrices Following Application of [Phenyl-UL-^{14}C]Isoxaflutole at 0.19 lb ai/A.

Compound	Corn Forage		Corn K+CWHR		Corn Grain		Corn Stover	
	TRR = 0.081 ppm		TRR = 0.010 ppm		TRR = 0.015 ppm		TRR = 0.120 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Isoxaflutole	--	--	--	--	--	--	--	--
RPA 203328	67.2[1]	0.056	60.9	0.005	63.0	0.010	63.3[2]	0.076
RPA 202248	--	--	6.5	<0.001	9.8	0.001	4.3	0.005
Unknowns	3.0	<0.001	--	--	--	--	11.8	0.014
Hexane soluble	1.3	0.001	0.6	<0.001	0.5	<0.001	0.9	0.001
Methanol:H_2O fractions not analyzed	6.2	0.005	2.6	<0.001	--	--	--	--
Aqueous soluble	15.1	0.012	25.7	0.003	4.0	0.001	7.8	0.009
ASE extracts	--	--	--	--	--	--	5.8	0.007
Total identified	67.2	0.056	67.4	0.007	72.8	0.011	67.6	0.081
Total characterized	25.6	0.021	28.9	0.003	4.5	0.001	26.3	0.032
Total extractable	92.9	0.075	96.3	0.009	77.3	0.012	93.7	0.112
Unextractable[3]	7.1	0.006	3.7	<0.001	22.7	0.003	6.3	0.008
Accountability[4]	100.0		100.0		100.0		100.0	

[1] Includes 15.4% TRR (0.013 ppm) that was identified after base hydrolysis of aqueous soluble residues.
[2] Includes 4.1% TRR (0.005 ppm) that was identified after base hydrolysis of aqueous soluble residues.
[3] Residues remaining after exhaustive extractions.
[4] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

C.3. Proposed Metabolic Profile

Based on the submitted corn metabolism study, the petitioner proposed that metabolism of isoxaflutole in corn proceeds via cleavage of the isoxazole ring resulting in RPA 202248, which is isomeric with the parent. RPA 203328 results from cleavage of the carbonyl bridge and loss of the complete isoxazole moiety.

The same metabolites were observed in an earlier corn study in which isoxaflutole was applied using both preplant incorporated and preemergence methods, without the addition of the safener cyprosulfamide (DP#s 214199 and 214212, 12/7/95, P. Errico). In that study, RPA 203328 was the major metabolite in all matrices (field corn forage, fodder, and grain), at 64-91% TRR. RPA 202248 was found in all matrices at <1% TRR, with the exception of grain from the preplant incorporated trial where RPA 202248 was found at 7.5% TRR. Isoxaflutole was not found in any matrix.

FIGURE C.3.1. Proposed Metabolic Profile of Isoxaflutole in Corn

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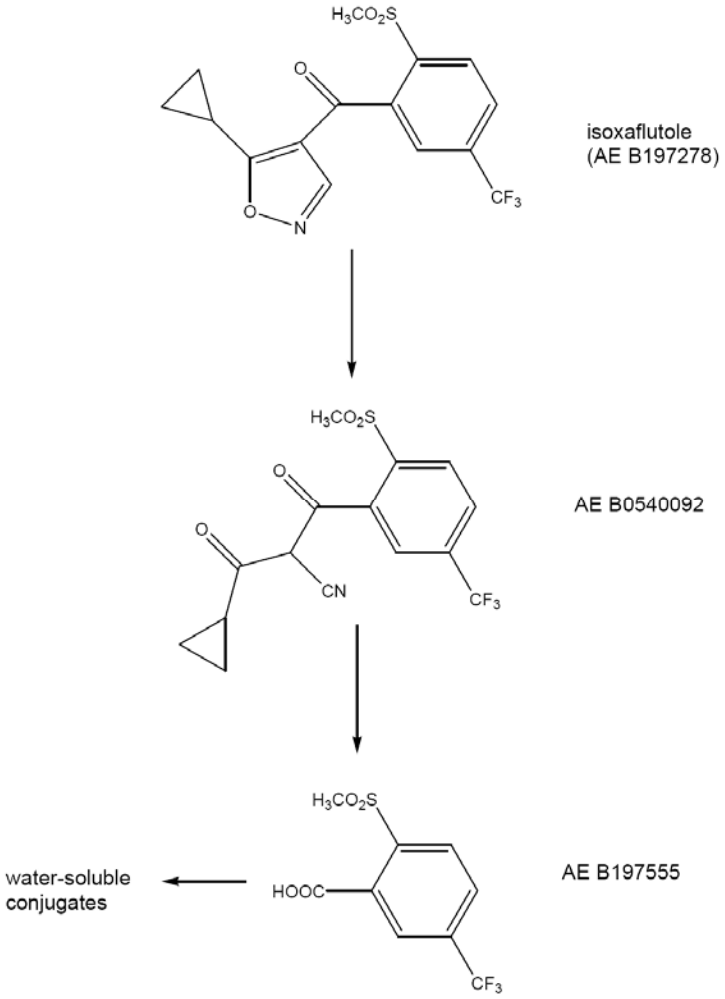
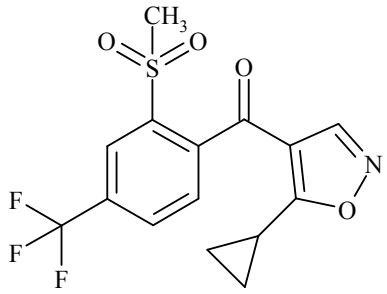
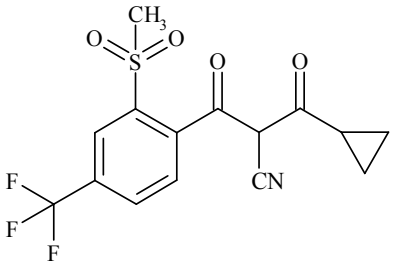
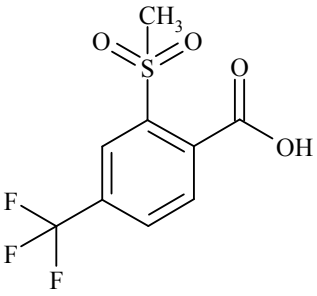


TABLE C.3.1. Identification of Compounds from Metabolism Study		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Isoxaflutole; AE B197278; RPA 201772	(5-cyclopropyl-4-isoxazolyl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone	
Isoxaflutole diketonitrile; AE B0540092; RPA 202248	1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione	
Isoxaflutole acid; AE B197555 RPA 203328	2-methylsulfonyl-4-trifluoromethyl benzoic acid	

D. CONCLUSION

Following a single foliar broadcast application of [phenyl-UL-^{14}C]isoxaflutole at 0.19 lb ai/A, TRR were 0.081 ppm in corn forage, 0.010 ppm in corn K+CWHR, 0.015 ppm in mature corn grain, and 0.120 ppm in corn stover.

RPA 203328 was the primary residue identified in all samples, accounting for 67.2% TRR in corn forage, 60.9% TRR in corn K+CWHR, 63.0% TRR in mature corn grain, and 63.3% TRR in corn stover. The only other identified metabolite was RPA 202248, which accounted for 6.5% TRR in corn K+CWHR, 9.8% TRR in mature corn grain, 4.3% TRR in corn stover; RPA 202248 was not identified in corn forage. Parent isoxaflutole was not identified in any corn matrix. The remainder of the radioactivity consisted of unknowns, totaling ≤12% TRR (≤0.014 ppm), and aqueous soluble fractions, totaling ≤26% TRR (≤0.016 ppm).

No supporting storage stability data are required, as the samples were analyzed within 6 months of collection.

Based on the submitted study, the petitioner proposed that metabolism of isoxaflutole in corn proceeds via cleavage of the isoxazole ring resulting in RPA 202248, which is isomeric with the parent. RPA 203328 results from cleavage of the carbonyl bridge and loss of the complete isoxazole moiety.

E. REFERENCES

DP#: 214199 and 214212
Subject: 264-EUP-00/PP#5G4484. Proposed Temporary Tolerance Request For Isoxaflutole in/on Field Corn Grain. Evaluation of Analytical Method and Residue Data. CBTS#'s 15430 & 15431.
From: P. Errico
To: D. Kenny/J. Miller
Date: 12/7/95
MRIDs: 43573201-43573208, 43573249-43573253, and 43588003

DP#: 224213
Subject: PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. Evaluation of Residue Data and Analytical Methods. Chemical 123000. CBTS# 17015. Case 287353.
From: G.F. Kramer
To: C. Eiden/D. McCall
Dated: 8/14/96
MRIDs: 43904801, 43904802, 43904827-43904837, and 43904839

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (4/2/08)
Petition Number: Not applicable
DP#s: 340598 and 340678
PC Code: 123000

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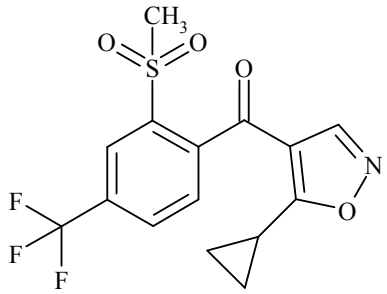
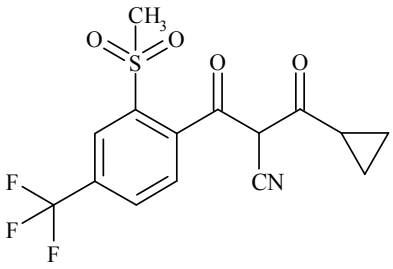
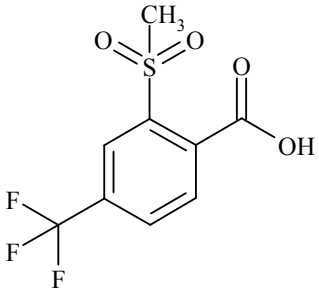
APPENDIX I. Chemical Names and Structures of Reference Standards Used in Corn Metabolism Study.		
Common name; Company code	Chemical name	Chemical structure
Isoxaflutole; AE B197278; RPA 201772	(5-cyclopropyl-4-isoxazolyl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone	
Isoxaflutole diketonitrile; AE 0540092; RPA202248	1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione	
Isoxaflutole acid; AE 197555 RPA 203328	2-methylsulfonyl-4-trifluoromethyl benzoic acid	
Uncyclized isoxaflutole; AE 0692291 RPA 205834	(2E)-2-(aminomethylene)-1-cyclopropyl-3-[2-mesyl-4-(trifluoromethyl)phenyl]propane-1,3-dione